(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 May 2001 (25.05.2001)

PCT

(10) International Publication Number
WO 01/35940 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/GB00/04363

(22) International Filing Date:
16 November 2000 (16.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9927121.5 16 November 1999 (16.11.1999) GB
0013238.1 31 May 2000 (31.05.2000) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/35940 A2

(54) Title: NOVEL COMPOSITION AND USE

(57) Abstract: A pharmaceutical composition comprising a thiazolidinedione metformin hydrochloride, and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated upon the surface of the metformin hydrochloride and the use of such composition in medicine.

NOVEL COMPOSITION AND USE

This invention relates to novel compositions, in particular to compositions containing more than one active ingredient and their use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Biguanide antihyperglycaemic agents are commonly used in the treatment of non-insulin dependent diabetes mellitus (NIDDM, or Type II diabetes). 1,1-Dimethylbiguanidine (or metformin) is an example of a biguanide antihyperglycaemic agent.

European Patent Application Publication Number 0 306 228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0 306 228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter referred to as "Compound (I)"). European Patent 0 658 161 discloses certain salts of Compound (I) including the maleate salt at Example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as "insulin sensitisers". In particular Compound (I) is a thiazolidinedione insulin sensitiser.

The above mentioned publications are incorporated herein by reference.

An important consideration in the preparation of formulations containing a combination of active agents is the stability of the active agents given that mutual interaction of the agents themselves or the agents with excipients can lead to instability of the agents.

Metformin is most commonly administered in the form of its hydrochloride salt (or metformin HCl). It is indicated that in certain formulations Compound (I) is prone to decomposition, both during preparation and storage, due to the presence of metformin hydrochloride We now provide pharmaceutical compositions containing Compound (I) and metformin hydrochloride in which the instability of Compound (I) is inhibited or prevented.

Accordingly, the invention provides a pharmaceutical composition comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride, and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated upon the surface of the metformin hydrochloride.

Suitably the thiazolidinedione is formulated as a thin layer upon the surface of the metformin hydrochloride

In a preferred aspect, the metformin hydrochloride is in a compacted form, such as a tablet form.

Preferably, the composition also comprises an inert barrier layer between the layer containing thiazolidinedione and the metformin hydrochloride.

The compositions so produced are multilayer compositions, generally bilayer compositions (wherein one active agent is applied, generally in a liquid form and usually directly, to the surface of the solid form of the other active agent), however the compositions may also comprise trilayer or tetralayer compositions (or indeed higher

multilayers) wherein repeated layers of each active are formed, preferably separated by an inert barrier layer.

Suitable dosages, preferably unit dosages, of the thiazolidinedione, such as Compound (I,) and metformin hydrochloride include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

The dosages of each particular active agent in any given composition can as required vary within a range of doses known to be required in respect of accepted dosage regimens for that compound.

In one particular aspect, the composition comprises 2 to 12 mg of Compound (I).

Suitably the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4 , 4 to 8, or 8 to 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4mg of Compound (I).

Particularly, the composition comprises 4 to 8mg of Compound (I).

Particularly, the composition comprises 8 to 12 mg of Compound (I).

Preferably, the composition comprises 2 mg of Compound (I).

Preferably, the composition comprises 4 mg of Compound (I).

Preferably, the composition comprises 8 mg of Compound (I).

As indicated above the unit doses of metformin include those found in the reference texts mentioned herein and include the doses set out below.

A suitable dosage of metformin hydrochloride is between 100 to 3000mg, for example 250, 500mg, 850mg, or 1000mg.

A suitable dosage of metformin hydrochloride is between 100 to 3000mg, for example 250, 500mg, 850mg, or 1000mg.

Particular compositions of the invention comprise doses of Compound (I) in the range of from 2-12mg and metformin hydrochloride in the range of from 100 to 3000mg, for example 4mg of Compound (I) and 500mg of metformin hydrochloride. Other formulations comprise 2mg of Compound (I) and 500mg or 850mg of metformin hydrochloride or 4mg of Compound (I) and 850mg of metformin hydrochloride.

Other thiazolidinediones include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone).

The compounds mentioned herein, in particular the thiazolidinediones such as Compound (I), may exist in one of several tautomeric forms, all of which are encompassed by the invention as individual tautomeric forms or as mixtures thereof. The

compounds mentioned herein may contain one or more chiral carbon atoms and hence can exist in two or more stereoisomeric forms, all of which are encompassed by the invention either as individual isomers or as mixtures of isomers, including racemates.

It will be understood that the thiazolidinedione, such as Compound (I) and metformin are in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate to the relevant pharmaceutically active agent chosen. In certain instances herein the names used for the antidiabetic agent may relate to a particular pharmaceutical form of the relevant active agent. It will be understood that all pharmaceutically acceptable forms of the active agents *per se* are encompassed by this invention.

Suitable pharmaceutically acceptable forms of the thiazolidinedione, such as Compound (I), and metformin include known pharmaceutically acceptable forms. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above mentioned publications. For example, a particular form of metformin is metformin hydrochloride.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0 306 228 and WO 94/05659, especially pharmaceutically acceptable salted or solvated forms. A preferred pharmaceutically acceptable salt form of Compound (I) is a maleate. A preferred pharmaceutically acceptable solvated form of Compound (I) is a hydrate. A preferred form of pioglitazone is as the hydrochloride salt.

Metformin is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0 306 228 and WO 94/05659. The disclosures of EP 0 306 228 and WO 94/05659 are incorporated herein by reference.

When used herein the term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance, impaired fasting glucose and hyperinsulinaemia.

"Conditions associated with diabetes mellitus itself" include hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin

resistance include polycystic ovarian syndrome, steroid induced insulin resistance and gestational diabetes.

"Complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term "pharmaceutically acceptable" embraces both human and veterinary use. For example, the term "pharmaceutically acceptable" embraces a veterinarily acceptable compound.

As used herein the term "liquid form" includes solutions and suspensions.

For the avoidance of doubt, unless other wise stated, when reference is made herein to scalar amounts, including mg amounts, of the active compound such as Compound (I), in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of the active compound *per se*. For example, 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt that provides 2 mg of Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390, and Frank P., "Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements", Clinical Products 1988.

The compositions may be in the form of tablets, lozenges, suppositories, or capsules. Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example sublingual or transdermal administration.

In a further aspect the invention also provides a process for preparing a pharmaceutical composition comprising a thiazolidinedione, such as Compound (I), metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated onto the surface of the metformin hydrochloride, which process comprises:

(i) formulating the metformin hydrchloride as required, preferably into a compacted form;

(ii) formulating the thiazolidinedione onto the surface of the metformin HCl.

Suitable carriers for the metformin hydrochloride comprises one or more components selected from: a binding agent, preferably PVP, a filler, a lubricants, a glidant, a disintegrant and a wetting agent.

The carrier for the metformin hydrochloride is as indicated preferably PVP but optionally at least one additional binder, for example hydroxypropylmethyl cellulose (or HPMC) is also used. In a particular preferred aspect when an additional binder or binders are used then the amount of PVP is the minimum required providing the required compressibility for metformin.

Generally the thiazolidinedione is dissolved or dispersed in a liquid and then applied to the surface of the metformin HCl.

The liquid may be water or a suitable organic solvent, such as ethanol.

Suitably a film-coating agent such as Opadry, is admixed with the thiazolidinedione solution or dispersion and this is applied to the surface of the metformin HCl. Alternatively, the thiazolidinedione solution or dispersion is applied to the metformin HCl and then the solution or dispersion of film coating agent is applied.

Preferably, the compositions are in unit dosage form. Unit dosage presentation forms for oral administration may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants and wetting agents.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, and tragacanth.

Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, and xylitol.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, and zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, and talc.

Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrilin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, and sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate.

As required the compositions may be prepared by conventional methods of blending, tabletting, or encapsulation. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

As indicated the compositions are formulated according to conventional methods, such as those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

The invention also provides a composition according to the invention for use in a method for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

No adverse toxicological effects are expected for the compositions of the invention in the above mentioned dosage ranges.

The following examples illustrate the invention but do not limit it in any way.

Examples

Example 1. Aqueous and non Aqueous Film Coating

Compound I is added to an Opadry coating suspension and applied to the surface of a preformed metformin tablet.

The Opadry I barrier and sealing coat are of identical formulation and are prepared as 15% w/w solid suspension.

The Opadry I plus Compound (I) suspension is prepared as a 15% w/w solid suspension with a 2:1 ratio of Opadry to Compound (I).

Metformin HCl tablet (equivalent to 500mg metformin HCl)

Formed by compression of granules of metformin HCl

Granules of metformin HCl	mg
Metformin HCl	500
Polyvinylpyrrolidone	15
Magnesium stearate	5

or

Granules of Metformin HCl	
Metformin HCl	500
Polyvinylpyrrolidone	15
HPMC	20
Magnesium stearate	2.5

Opadry Barrier Coat	% w/w
Opadry I solids	15
Water	85

Opadry plus Compound (I)	% w/w
Opadry I solids	10
Compound (I)	5
Water	85

Opadry Sealing Coat

As Opadry I Barrier Coat

Formula	mg/tab
Metformin HCl tablet (equivalent to 500mg metformin HCl)	520
Opadry Barrier Coat (1% of tablet core)	5.20
Opadry plus Compound (I) (equivalent to 4mg Compound (I))	15.90
Opadry I Sealing Coat (2% of tablet core)	10.80

Claims.

1. A pharmaceutical composition comprising a thiazolidinedione metformin hydrochloride, and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated upon the surface of the metformin hydrochloride.

2. A composition according to claim 1, wherein the metformin hydrochloride is in a compacted form.

3. A composition according to claim 1 or claim 2, wherein the thiazolidinedione is formulated as a thin layer upon the surface of the metformin hydrochloride.

4. A composition according to any one of claims 1 to 3, wherein the composition also comprises an inert barrier layer between the layer containing thiazolidinedione and the metformin hydrochloride.

5. A composition according to any one of claims 1 to 4, wherein composition is in the form of a multilayer composition.

6. A composition according to any one of claims 1 to 5, wherein the composition is in the form of a tablet.

7. A composition according to any one of claims 1 to 6, wherein the carrier for the metformin hydrochloride comprises one or more components selected from: a binding agent being PVP, a filler, a lubricant, a glidant, a disintegrant and a wetting agent.

8. A composition according to claim 7, wherein the carrier for the metformin hydrochloride comprises at least one additional binder.

9. A composition according to claim 7, wherein the amount of PVP is the minimum amount that provides the required compressibility for metformin hydrochoride.

10. A composition according to any one of claims 1 to 9, wherein thiazolidinedione is selected from: Compound (I) or include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone), especially 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

11. A composition according to any one of claims 1 to 10, wherein the composition comprises 2 to 12 mg of Compound (I).

12. A composition according to any one of claims 1 to 10, wherein the composition comprises 100 to 3000mg of metformin hydrochloride.

13. A process for preparing a pharmaceutical composition comprising a thiazolidinedione, metformin hydrochloride and a pharmaceutically acceptable carrier, wherein the thiazolidinedione is formulated onto the surface of the metformin hydrochloride, which process comprises:
(i) formulating the metformin HCl as required;
(ii) formulating the thiazolidinedione onto the surface of the metformin hydrochloride.

14. A composition according any one of claims 1 to 12, for use in a method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus.